

# Abuse/Misuse of Prescription Medications in Older Adults



Esra Ates Bulut, MD<sup>a</sup>, Ahmet Turan ISIK, MD<sup>b,\*</sup>

## KEYWORDS

- Inappropriate prescribing • Misuse • Abuse • Older adults • Opioids
- Benzodiazepines • Chronic pain

## KEY POINTS

- With the increasing aged population, drug misuse and abuse are increasing in these patients.
- Central nervous system depressants, opioids, and stimulants are potential drugs for abuse in patients.
- Although the rate of illicit drug use is low in older adults, the rate of prescription drug abuse increases in women, those with social isolation, those with depression, and those with previous substance abuse.
- Sleep disorders (insomnia) and mental health issues, frequently reported in older patients, play an essential role in prescribing sedative and anxiolytic medications.
- Drug abuse and misuse and complications related to these conditions should be considered in the rationalization of pharmacotherapy in geriatric cases, primarily due to their preventable potential.

## POLYPHARMACY AND APPROPRIATE PRESCRIBING

Depending on developing health technologies, medications, and preventive medicine practices, life expectancy is gradually increasing, and the world population is getting older. The frequent occurrence of chronic diseases such as diabetes mellitus, coronary artery disease, hypertension, cerebrovascular disease, and neurocognitive disorders in older adults makes the use of multiple drugs (polypharmacy) an important problem in geriatric practice. Although polypharmacy is defined as “unnecessary drug use or the administration of more drugs than clinically indicated,”<sup>1</sup> the use of more than four drugs at the same time is generally considered to be polypharmacy

<sup>a</sup> Department of Geriatric Medicine, Adana City Training and Research Hospital, Adana, Turkey;

<sup>b</sup> Unit for Brain Aging and Dementia, Department of Geriatric Medicine, Dokuz Eylul University, School of Medicine, 35340 Balcova, IZMIR, Turkey

\* Corresponding author.

E-mail address: [atisik@yahoo.com](mailto:atisik@yahoo.com)

and the use of ten or more drugs at the same time as hyperpolypharmacy.<sup>2</sup> Even though the prevalence of polypharmacy is reported to be between 37% and 58% in community-dwelling older adults,<sup>3</sup> the rate reaches 80% in those staying in the nursing home.<sup>4</sup> Appropriate polypharmacy is defined as optimizing the treatment of patients according to the evidence in the presence of many medical diseases or in complex conditions. On the other hand, inappropriate polypharmacy is the use of multiple drugs with high risk of side effects but with low benefit from treatment.<sup>5</sup>

There are many factors that contribute to polypharmacy in the older adults. The adverse effects associated with these drugs play a very important role in the emergence of the condition known as the prescribing cascade, which is perceived as a new medical condition and increases the drug burden.<sup>6</sup> For example, for constipation, urinary retention, and abdominal pain that may develop with the use of tricyclic antidepressants, new symptomatic treatments for the side effects can be added instead of discontinuing the tricyclics. Moreover, older adults, who frequently take over-the-counter medications, vitamins, and nutritional supplements, tend not to list them when reviewing medications by health care professionals, which both increases the drug burden and causes unwanted drug interactions.<sup>7</sup> Pharmacokinetic and pharmacodynamic changes that develop due to aging increase the risk of adverse drug reactions. Changes occur in the distribution of drugs in the body due to metabolism in the liver, elimination in the kidneys, and changes in body composition (partial increase in adipose tissue with reduced muscle mass). However, the decrease in physiologic reserves in the organ systems in frail patients and the difficulty in the management of multiple systemic diseases easily lead to undesirable consequences.<sup>8</sup> Studies have shown that polypharmacy, a geriatric syndrome, is associated with the increased frequency of different geriatric syndromes such as frailty, malnutrition, gait and balance disorders, falls, cognitive impairment, depression, urinary incontinence, as well as nursing home placement, increased frequency of hospital admissions, decreased functional capacity, activities of daily living and deterioration in the quality of life, and increased health expenditures.<sup>3,9,10</sup> Increased age, presence of concomitant systemic diseases, cognitive impairment, psychological problems (mental health conditions), long-term care facility residency, referral to doctors in different branches (multiple subspecialists), and disabilities appear as risk factors for polypharmacy.<sup>11</sup> The most important risk factor is the high number of drugs prescribed.<sup>12</sup> Polypharmacy not only economically burdens the health care system but also reduces the patient's drug compliance and increases prescribing of potentially inappropriate medications, drug misuse, drug-drug interactions, and the risk of adverse drug events (ADEs), ADE-related hospitalization, and even mortality.<sup>13</sup> In a study where 27,617 elderly outpatient applications were examined in a 12-month period, it was reported that the rate of ADE was 5.5%, of which 27.6% were preventable.<sup>14</sup> Some drug groups, such as those often prescribed for older patients, especially those that act on the central nervous system, potentially cause more side effects. In addition to these disadvantages related to pharmacotherapy in geriatric cases, it should also be taken into account that misuse and abuse of prescription drugs are serious problems with a considerable frequency.<sup>15</sup> Therefore, various guidelines and scales have been developed to optimize the medical treatment of elderly patients with many complex medical conditions that are vulnerable to adverse effects of the drugs. In these scales and guidelines, drugs that are not recommended for use in the elderly, potential interactions between drugs, appropriate and inappropriate treatments according to the clinical situation are specified. Prescribing guidelines have been developed for a wide range of classes, including anticholinergic, antiparkinsonian, antispasmodic, antithrombotic, anti-infective, antidepressant, antipsychotic, sedative/hypnotic, analgesics,

and cardiovascular, gastrointestinal, and genitourinary system drugs.<sup>12</sup> The most well-known tools in use to support appropriate prescribing in older patients are summarized in **Box 1**. It is unclear whether these tools have made clinically significant improvements in meta-analyses, but it is obvious that they reduce inappropriate prescribing.<sup>16,17</sup>

Drug evaluation and optimization of medical treatment is an important part of the comprehensive geriatric assessment (CGA), accepted as the gold standard, which allows for the evaluation of older adults in a holistic and patient-centered manner. It has been reported that the frequencies of polypharmacy and hyperpolypharmacy after CGA application decreased from 56% to 34% and from 12% to 3%, respectively.<sup>2</sup> Considering the drug groups whose frequency of use has decreased after CGA, it is noteworthy that there are antihistamines, proton pump inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), drugs initiated for dizziness, antiemetic drugs, pre-meal short-acting insulins, digoxin, benzodiazepines, antipsychotics, and anti-dementia drugs. Thus, it is shown that by discontinuing unsuitable drugs, savings of \$ 153/year per capita, an expenditure of \$ 67/year per capita by initiating indicated treatments, and net savings of \$ 86/year per capita were provided.<sup>2</sup>

When prescribing in older adults, it is recommended to avoid drug groups with anticholinergic effects. Anticholinergic drug groups include bladder antispasmodics, first-generation antihistamines, tricyclic antidepressants, skeletal muscle relaxants, antiemetics, and antipsychotics.<sup>12</sup> Anticholinergic Drug Scale,<sup>23</sup> Anticholinergic Risk Scale,<sup>24</sup> Anticholinergic Cognitive Burden Scale,<sup>25</sup> and Drug Burden Index<sup>26</sup> to evaluate the cholinergic burden in the treatment of patients provide the opportunity to better examine the relationship between negative results that occur with exposure to anticholinergic side effects, rather than looking at individual drugs or drug classes separately. Anticholinergic effects, counted as confusion, hallucination, dry mouth, blurred vision, constipation, nausea, urinary retention, sweating, and tachycardia, pose a risk for falls, delirium, cognitive impairment, decreased physical performance, and mortality in elderly patients.<sup>27,28</sup>

It is necessary to prevent inappropriate polypharmacy in older patients to increase patients' adherence to treatment (ensure drugs are used at the desired dose at correct intervals to get the most benefit from medical treatment). The existence of a safer alternative to the regimen applied, adverse effects, toxicity, and the suitability of the patients to come for follow-up should be reviewed separately. Patients should be adequately informed about their medical conditions, their concerns about treatment should be eliminated, and drug use motivation should be provided. If possible, the number of daily drug doses should be minimized in terms of drug compliance by using appropriate combined preparations in which two or more drugs are used together at

#### Box 1

##### Assessment tools of prescribing appropriateness

American Geriatrics Society (AGS) Beers Criteria<sup>12</sup>

Screening Tool to Alert doctors to Right Treatment (START) and/or the Screening Tool of Older People's Prescriptions (STOPP)<sup>18</sup>

Fit FOR The Aged-FORTA<sup>19</sup>

Medication Appropriateness Index<sup>20</sup>

Assessing Care of Elders (ACOVE)<sup>21</sup>

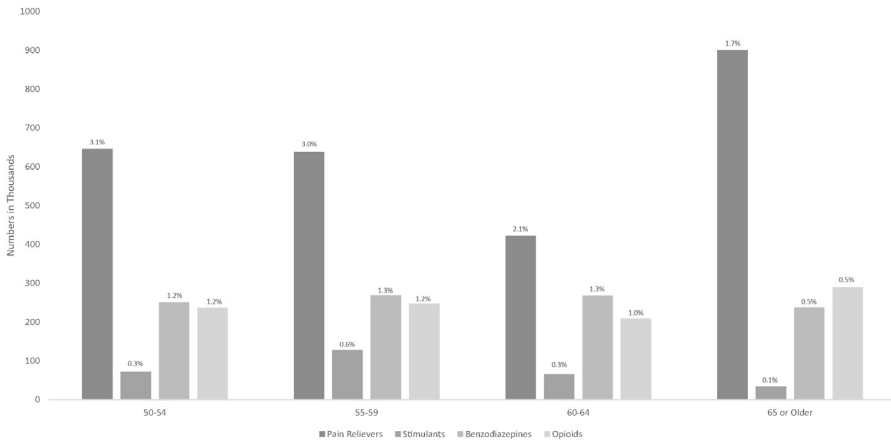
PRISCUS List<sup>22</sup>

the same time.<sup>29</sup> In older adults with cognitive and physical disabilities and vision and hearing problems, treatment should be specifically arranged, and in some cases, the help of caregivers may be needed.

## PRESCRIPTION DRUG ABUSE AND MISUSE

It has been previously stated that misuse and abuse of prescription drugs is a serious problem in older patients. Because older people are not at the forefront in social, legal, and professional areas, it is a little more difficult to notice substance and drug abuse in these people.<sup>15</sup> The National Institute on Drug Abuse defines drug abuse as “the intentional use of a medication without a prescription; in a way other than as prescribed; or for the experience or feeling it causes”.<sup>30</sup> The Food and Drug Administration (FDA) describes misuse as the use of pharmaceutical medication that is, contrary to medical advice or that is, not as prescribed.<sup>30</sup> Misuse of medicines includes consuming extra doses, not refilling prescriptions, misunderstanding the doctor’s instructions, underdosing, and taking medications at the wrong time. Chronic diseases in the older population, changes in drug metabolism, and increased potential for drug interactions make the abuse and misuse of drugs (and other substances) more dangerous than in the younger population.<sup>31</sup> Problems such as chronic pain in patients may make long-term use of many drugs such as opioids and NSAIDs inevitable. Therefore, although it is difficult to use drugs appropriately, economic inadequacies in these cases may increase the tendency of patients to use other patients’ drugs. However, risky behaviors such as obtaining prescriptions from more than one doctor or storing medication over time are issues that should be questioned, especially in geriatric cases.<sup>32</sup> Thus, compliance with the treatment is negatively affected in geriatric cases, and older adults cannot benefit from the treatment effectively due to misuse. Although the rate of illicit drug use is low in the elderly, the rate of drug abuse increases in women, those with social isolation, depressives, and those who had previous substance abuse.<sup>32</sup> In older individuals, loss of status after retirement, decreased social support, financial difficulties, limited physical mobility, loneliness after loss of spouse and close friends, or encountering serious health conditions have been shown to be associated with inappropriate drug use.<sup>15</sup> In the United States (USA), it is estimated that at least one in four older people has a prescription for psychoactive drugs that are open to potential misuse.<sup>33</sup> According to the 2019 National Survey on Drug Use and Health, the frequency of prescription drug misuse in the last year for those aged 50 years and older is given in **Fig. 1**.<sup>34</sup> Common sleep disorders (insomnia) and mental problems in older patients play an important role in prescribing sedative and anxiolytic prescriptions for these cases.<sup>35</sup> In particular, benzodiazepines and opioid analgesics are prescribed for a long time, thus increasing the frequency of side effects associated with these drugs. For example, it has been reported that long-term use of benzodiazepines increases the risk of falls, hip fractures, and traffic accidents, as well as increases the risk of addiction.<sup>36</sup>

Prescription or over-the-counter drug abuse requires attention because of the potential negative consequences. Using drugs that reduce respiratory rate such as central nervous system depressants and opioids, antihistamines, and general anesthetics, especially alcohol, psychotropic, and narcotics, deepens respiratory depression. The increase in prescription drug abuse and misuse increases emergency room visits, overdose deaths, drug use disorders, and treatment applications for addiction.<sup>37</sup>



**Fig. 1.** Misuse of prescribed drugs in past year 2019. (Data from Center for Behavioral Health Statistics and Quality. (2020). Results from the 2019 National Survey on Drug Use and Health: Detailed tables. Rockville, MD: Substance Abuse and Mental Health Services Administration. Retrieved from <https://www.samhsa.gov/data/>.)

Substance-Related Disorder title has been changed as Substance-Related and Addictive Disorders in the Diagnostic and Statistical Manual 5th edition (DSM-5) criteria. Combining abuse and dependence criteria decreases confusion over diagnosis and leads to approach the issue in a broader context. The new 11-item diagnostic criteria are easy to implement in clinical settings yielding early identification and treatment of drug or alcohol problems. DSM-5 change makes it easier for primary care to be reimbursed by insurance to screen for alcohol and drug problems and conduct short counseling sessions.<sup>38</sup> The criteria are also merged to diagnose disorders related to the use of many drugs and substances. Subtitles are defined as alcohol, caffeine, cannabis, hallucinogen, inhalant, opioid, sedative, hypnotic or anxiolytic, stimulant, tobacco, and other (or unknown) substances-related disorders.<sup>39</sup> The drug groups with the most abused in this regard are summarized in **Table 1**.

### Opioids

They are used to reduce pain sensation through opioid receptors on the brain and spinal cord. In addition to their pain-reducing properties, they stimulate reward regions in the brain, causing euphoria, which explains the potential for misuse or abuse of opioids.<sup>40</sup> The opioid-analgesic poisoning mortality rate for adults aged 55 to 64 years rose from 1/100,000 in 1999 to nearly 6-fold to 6.3/100,000 in 2011.<sup>41</sup> Chronic pain is an important risk factor for suicide in the older adults, and opioid abuse rates are high in patients with chronic pain.<sup>42</sup> In the USA, the opioid epidemic was declared a national public health emergency in 2017.<sup>43</sup> State and federal policies have been established to reduce opioid prescription in chronic non-malignant pain. A long-term benefit of opioids in pain and function has not been demonstrated with current evidence, and there are no long-term studies to examine outcomes for chronic pain after at least 1 year.<sup>44</sup>

Opioids cause drowsiness, confusion, nausea, constipation, and respiratory depression. The risk of toxicity increases with misuse or abuse with alcohol and sedatives. In long-term regular use, addiction and tolerance may develop, and abrupt termination of use causes withdrawal symptoms. These symptoms include

Opiod analgesics	Hydrocodone Oxycodone Oxymorphone Morphine Codeine Fentanyl Meperidine Hydromorphone
Stimulants	Amphetamine Methylphenidate
Benzodiazepines	lprazolam Triazolam Chlorodiazepoxide Diazepam Lorazepam
Barbiturates	Pentobarbital Phenobarbital
Z-drugs	Zaleplon Zolpidem Eszopiclone
Antidepressants	Bupropion Venlafaxine
Antipsychotics	Quetiapine
Gabapentinoids	Pregabalin Gabapentin
Dopaminergic Drugs	Levodopa

Data from National Institute on Drug Abuse. Commonly Used Drugs Charts. <https://www.drugabuse.gov/drug-topics/commonly-used-drugs-charts#prescription-stimulants>. Accessed in 15th May 2021; and Chiappini S, Guirguis A, Corkery J, Schifano F. Understanding the use of prescription and OTC drugs in obtaining illicit highs and the pharmacist role in preventing abuse. *The Pharmaceutical Journal*. 2020.

restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes, and involuntary leg movements.<sup>45</sup> Various risk factors have been identified for opioid misuse and abuse, including sociodemographic factors, pain- and drug-related factors, genetics and environment, underlying psychopathology, and alcohol and substance use disorders. Women are at risk of misusing opioids due to emotional stressors, whereas men tend to abuse opioids for legal and problematic behavioral issues. Chronic physical conditions such as hypertension, arthritis, and arteriosclerosis have been associated with opioid abuse/addiction.<sup>46</sup> Although opioids can be prescribed for reasons other than pain in older adults, the most important opioid indication in this age group is pain. Studies have reported that the use of opioids for indications other than pain increases the risk of benzodiazepine misuse, suicidal ideations, and any substance use disorder in geriatric cases.<sup>47</sup>

### **Stimulants**

The number of stimulant prescriptions for attention deficit hyperactivity disorder has increased in recent years. Stimulants cause an increase in a person's alertness and energy levels, suppression of appetite, and euphoria. Some people use these

medications without medical indications to improve mental performance. However, stimulants may cause anxiety and agitation by increasing blood pressure, heart rate, and body temperature. Although misuse is rarely seen in those aged 50 years, their use in the older population is dangerous due to the cardiovascular problems caused by them.<sup>48</sup>

### **Sedatives**

---

Benzodiazepines are gamma aminobutyric acid (GABA) receptor agonists that provide sedative and anxiolytic effects, primarily used in the treatment of sleep disorders and anxiety. Benzodiazepines can cause euphoria, as well as reduce anxiety and aid sleep. Therefore, they are drugs that are open to abuse for recreational purposes. Long-term (>4 months) and/or high-dose (>10 mg/day diazepam equivalent) use of benzodiazepines is associated with the development of addiction.<sup>33</sup> Benzodiazepines with long half lives, such as flurazepam, are not recommended for use in older adults because of their association with sedative effects, falls, motor vehicle accidents, and memory problems. Withdrawal symptoms include increased heart rate, trembling of hands, insomnia, nausea, vomiting, and anxiety. Generalized seizures can occur in 20% to 30% of users who are not treated for withdrawal symptoms.<sup>33</sup> Long-term use of sedatives, especially benzodiazepines, is more common in women, perceived poor health, and patients with truly poor physical health.

Z-drugs have a different chemical structure, but they act on the same GABA type A receptors in the brain as benzodiazepines and are thought to have fewer side effects and less risk of addiction than benzodiazepines.<sup>49</sup> Barbiturates are classified as sedatives because of their central nervous system calming and sleep effects. The primary therapeutic indications for them are induction of anesthesia and treatment of epilepsy. Most of those who abuse them have experienced other sedatives as well because addiction to them alone is rare.<sup>50</sup>

### **Antidepressants**

---

Among antidepressants, the dopaminergic effects and stimulant-like activities of bupropion may explain the potential misuse value. In the literature, the recreational use of it is defined as bupropion abuse, including nasal insufflation of crushed tablets and intravenous injection.<sup>51</sup> Venlafaxine is an antidepressant that is a serotonin-norepinephrine reuptake inhibitor. High doses are taken for amphetamine/ecstasy-like euphoria and dissociative effects such as distorted sense of time and numbness. Overdose deaths associated with tachycardia, seizures, coma, and serotonin syndrome have been reported, and addiction problems have been described after prolonged use.<sup>52</sup>

### **Antipsychotics**

---

Quetiapine is the most abused second-generation antipsychotic because of its sedative and anxiolytic properties. Although the FDA approved its use for schizophrenia and certain types of bipolar and depressive disorders, off-label use is also common for anxiety, depression, dementia behavioral disorders, sleep disorder, and substance use disorder. Information on the misuse of quetiapine is accumulating in the literature. Emergency room admissions for its abuse were reported to almost double between 2005 and 2011.<sup>53</sup> It has been reported that quetiapine misuse is more common in substance abusers or misusers because of its anxiolytic and sedative effects.<sup>54,55</sup>

### ***Gabapentinoids***

---

Gabapentin and pregabalin are used in the treatment of neuropathic pain, fibromyalgia, restless leg syndrome, and epilepsy. They are prescribed off-label in alcohol/narcotic withdrawal and non-neuropathic pain disorders. Gabapentin binds to the auxiliary  $\alpha$ -2-delta subunit of a voltage-dependent calcium channel, which decrease inward calcium currents and consequently attenuate central neuronal excitability.<sup>56</sup> Pregabalin has a much higher binding affinity for the  $\alpha$ 2- $\delta$  subunit and potency than that of gabapentin. Opioid users frequently abuse pregabalin to achieve the desired psychoactive effect (eg, potentiate heroin/cocaine effects), combat opioid withdrawal symptoms, and reduce physical pain.<sup>57</sup> There are reservations for gabapentinoids such as increasing prescription levels over time, users seeing this molecule as an alternative to illegal substances, and increasing drug-related deaths from various countries.<sup>58</sup>

### ***Dopaminergic Agents***

---

Levodopa is often used as a replacement therapy to control motor symptoms in the treatment of Parkinson disease. During the treatment, an impulse control disorder called dopamine dysregulation syndrome (DDS) may be observed, which may cause misuse of dopaminergic drugs by stimulating the central nervous system structures involved in reward signaling including the mesocortical and mesolimbic system. Intake of dopaminergic drugs in higher doses than necessary to control motor symptoms may result in demand for higher doses to the physician.<sup>59</sup> Patients can also misuse levodopa and dopamine agonists. It is stated that personal depressive symptoms and a family or personal history of drug abuse increase the risk for DDS.<sup>60</sup>

## **PREVENTION AND TREATMENT OF DRUG ABUSE IN OLDER ADULTS**

Cognitive problems and psychomotor disorders associated with the use of benzodiazepines and opioids in older adults are common. Defining substance abuse problems in older ages becomes more difficult as signs of addiction or intoxication may appear similar to depression, anxiety, delirium, or dementia or can be attributed to the effects of aging.<sup>61</sup> It should also be noted that health care professionals are less skeptical of abuse in older patients, and as a result, issues related to drug misuse or abuse may not have been adequately reported in patients. Besides, the lack of diagnostic tools and the indistinct clinical consequences of abuse on elderly patients may cause drug abuse to be overlooked.

It would be helpful for medication management for older adults to always have a chart with information about prescription and nonprescription medications that they can share with their health care providers. Limiting exposure to potentially abusive drugs or choosing safer alternative treatments, if possible, involves limiting dose, duration, or number of prescriptions.<sup>62</sup> The effectiveness and adherence to the treatment should be evaluated at regular intervals by informing the patient and their relatives about the side effects of the treatment and the potential for abuse. It is necessary to integrate misuse and abuse screening with cognitive assessment into routine health care to provide comprehensive evaluation tailored to the needs of older patients with multiple needs. Health care professionals should be aware of possible deviations from prescription drugs, recognize cases of abuse and misuse, and design safe treatment regimens for individuals as much as possible, taking into account the possibility of multiple drug abuse.<sup>63</sup> Prescribing should be made in accordance with guidelines to monitor the benefits and risks of chronic opioid therapy.<sup>44</sup>



The lack of validated tools to assess prescription drug problems in older adults leads to underestimation of the prevalence of such problems. However, it has been reported that various irregularities are attempted by the patients and their relatives in order to reach the drugs, which puts a serious economic burden on the health care system. For this reason, electronic data-based prescription drug monitoring programs have been developed in many countries to monitor controlled substances and to inform doctors and pharmacists about this issue.<sup>64</sup>

Treatments aimed at increasing social support and self-esteem are acceptable interventions to reduce problematic prescription drug use. This approach includes identifying causes of non-compliance, informing patients about the importance of following medication management and dosing instructions, and describing the health and functional consequences of prescription drug abuse. Furthermore, encouraging the participation of family members in the treatment process can be effective in increasing the chance of success.<sup>33</sup> Considering the possibility of more severe addiction and the risks of comorbid conditions associated with detoxification in older adults with substance and drug use problems, it should be kept in mind that a special approach is required for these patients. Clinicians should pay close attention to potential drug–drug and drug–disease interactions in older adults being treated for substance-related disorders.

## SUMMARY

Despite the evidence that older adults are particularly vulnerable to the misuse and abuse of drugs, insufficient information is available about the screening, evaluation, diagnosis, and treatment. Awareness of all health care professionals involved in the care and treatment of older patients should be increased regarding the problems of misuse and abuse of drugs.

## CLINICS CARE POINTS

- Appropriate prescribing is of particular importance in geriatric practice, and several tools have been developed.
- Prescription drugs, such as sedatives, opioids, gabapentinoids, have the potential to misuse or abuse.
- Awareness of the abuse or misuse of prescription drugs in older patients should be expanded because the situation could be easily overlooked, and there are no universally accepted screening and diagnostic tools.

## REFERENCES

1. Montamat SC, Cusack B. Overcoming problems with polypharmacy and drug misuse in the elderly. *Clin Geriatr Med* 1992;8(1):143–58.
2. Unutmaz GD, Soysal P, Tuven B, et al. Costs of medication in older patients: before and after comprehensive geriatric assessment. *Clin Interv Aging* 2018; 13:607–13.
3. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014;13(1):57–65.
4. Mahlknecht A, Krisch L, Nestler N, et al. Impact of training and structured medication review on medication appropriateness and patient-related outcomes in nursing homes: results from the interventional study InTherAKT. *BMC Geriatr* 2019;19(1):257.

5. Mair A, Fernandez-Llimos F. Polypharmacy management programmes: the SIM-PATHY Project. *Eur J Hosp Pharm* 2017;24(1):5–6.
6. Rochon PA, Gurwitz JH. The prescribing cascade revisited. *Lancet* 2017; 389(10081):1778–80.
7. Nahin RL, Pecha M, Welmerink DB, et al. Concomitant use of prescription drugs and dietary supplements in ambulatory elderly people. *J Am Geriatr Soc* 2009; 57(7):1197–205.
8. Baruth JM, Gentry MT, Rummans TA, et al. Polypharmacy in older adults: the role of the multidisciplinary team. *Hosp Pract (1995)* 2020;48(sup1):56–62.
9. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother* 2007;5(4):345–51.
10. Ates Bulut E, Soysal P, Isik AT. Frequency and coincidence of geriatric syndromes according to age groups: single-center experience in Turkey between 2013 and 2017. *Clin Interv Aging* 2018;13:1899–905.
11. Halli-Tierney AD, Scarbrough C, Carroll D. Polypharmacy: evaluating risks and deprescribing. *Am Fam Physician* 2019;100(1):32–8.
12. American geriatrics society 2019 updated AGS beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019;67(4): 674–94.
13. Piccoliori G, Mahlknecht A, Sandri M, et al. Epidemiology and associated factors of polypharmacy in older patients in primary care: a northern Italian cross-sectional study. *BMC Geriatr* 2021;21(1):197.
14. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003; 289(9):1107–16.
15. McLarnon ME, Barrett SP, Monaghan TL, et al. Prescription drug misuse across the lifespan: a developmental perspective. In: Verster JC, Brady K, Galanter M, et al, editors. *Drug abuse and addiction in medical illness: causes, consequences and treatment*. New York, NY: Springer New York; 2012. p. 213–30.
16. Cooper JA, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. *BMJ Open* 2015;5(12):e009235.
17. Rankin A, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev* 2018; 9(9):Cd008165.
18. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44(2): 213–8.
19. Kuhn-Thiel AM, Weiß C, Wehling M. Consensus validation of the FORTA (Fit for the Aged) list: a clinical tool for increasing the appropriateness of pharmacotherapy in the elderly. *Drugs Aging* 2014;31(2):131–40.
20. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol* 1992;45(10):1045–51.
21. Wenger NS, Shekelle PG. Assessing care of vulnerable elders: ACOVE project overview. *Ann Intern Med* 2001;135(8 Pt 2):642–6.
22. Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl Int* 2010;107(31–32):543–51.
23. Carnahan RM, Lund BC, Perry PJ, et al. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol* 2006;46(12):1481–6.

24. Rudolph JL, Salow MJ, Angelini MC, et al. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med* 2008;168(5):508–13.
25. Cai X, Campbell N, Khan B, et al. Long-term anticholinergic use and the aging brain. *Alzheimers Dement* 2013;9(4):377–85.
26. Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. *Arch Intern Med* 2007;167(8):781–7.
27. Brombo G, Bianchi L, Maietti E, et al. Association of anticholinergic drug burden with cognitive and functional decline over time in older inpatients: results from the CRIME project. *Drugs Aging* 2018;35(10):917–24.
28. Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2015;80(2):209–20.
29. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: "There's got to be a happy medium. *Jama* 2010;304(14):1592–601.
30. Smith SM, Dart RC, Katz NP, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTION systematic review and recommendations. *Pain* 2013;154(11):2287–96.
31. Cotto JH, Davis E, Dowling GJ, et al. Gender effects on drug use, abuse, and dependence: a special analysis of results from the National Survey on drug use and health. *Gen Med* 2010;7(5):402–13.
32. Culberson JW, Ziska M. Prescription drug misuse/abuse in the elderly. *Geriatrics* 2008;63(9):22–31.
33. Simoni-Wastila L, Yang HK. Psychoactive drug abuse in older adults. *Am J Geriatr Pharmacother* 2006;4(4):380–94.
34. Center for Behavioral Health Statistics and Quality. Results from the 2019 national survey on drug use and health: detailed tables. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2020. Available at: <https://www.samhsa.gov/data/>.
35. Prinz PN, Vitiello MV, Raskind MA, et al. Geriatrics: sleep disorders and aging. *N Engl J Med* 1990;323(8):520–6.
36. Griffiths RR, Johnson MW. Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. *J Clin Psychiatry* 2005;66(Suppl 9):31–41.
37. Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *Am J Prev Med* 2015;49(4):493–501.
38. Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry* 2013;170(8):834–51.
39. Association AP. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 2013.
40. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International expert panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract* 2008;8(4):287–313.
41. Chen LH, Hedegaard H, Warner M. Drug-poisoning deaths involving opioid analgesics: United States, 1999–2011. *NCHS Data Brief* 2014;(166):1–8.
42. Webster LR. Risk factors for opioid-use disorder and overdose. *Anesth Analg* 2017;125(5):1741–8.

43. U.S. Department of health and Human Services. U.S acting secretary declares public health emergency to address national opioid crisis 2017. Available at: <https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html>.
44. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016;315(15):1624–45.
45. Jones CM, Lurie PG, Throckmorton DC. Effect of US drug enforcement administration's rescheduling of hydrocodone combination analgesic products on opioid analgesic prescribing. *JAMA Intern Med* 2016;176(3):399–402.
46. Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: Part 1. *Pain Physician* 2017;20(2s):S93–109.
47. Schepis TS, Wastila L, Ammerman B, et al. Prescription opioid misuse Motives in US older adults. *Pain Med* 2020;21(10):2237–43.
48. Spiller HA, Hays HL, Aleguas A Jr. Overdose of drugs for attention-deficit hyperactivity disorder: clinical presentation, mechanisms of toxicity, and management. *CNS drugs* 2013;27(7):531–43.
49. Badrakalimuthu VR, Rumball D, Wagle A. Drug misuse in older people: old problems and new challenges. *Adv Psychiatr Treat* 2010;16(6):421–9.
50. Weaver MF. Prescription sedative misuse and abuse. *Yale J Biol Med* 2015;88(3):247–56.
51. Stall N, Godwin J, Juurlink D. Bupropion abuse and overdose. *CMAJ* 2014;186(13):1015.
52. Leonard JB, Klein-Schwartz W. Characterization of intentional-abuse venlafaxine exposures reported to poison control centers in the United States. *Am J Drug Alcohol Abuse* 2019;45(4):421–6.
53. Mattson ME, Albright VA, Yoon J, et al. Emergency department visits involving misuse and abuse of the antipsychotic quetiapine: results from the drug abuse warning network (DAWN). *Subst Abuse* 2015;9:39–46.
54. McLarnon ME, Fulton HG, Maclsaac C, et al. Characteristics of quetiapine misuse among clients of a community-based methadone maintenance program. *J Clin Psychopharmacol* 2012;32(5):721–3.
55. Cubata WJ, Springer J. Quetiapine abuse and dependence in psychiatric patients: a systematic review of 25 case reports in the literature. *J Substance Use* 2014;19(5):388–93.
56. van Hooft JA, Dougherty JJ, Endeman D, et al. Gabapentin inhibits presynaptic Ca(2+) influx and synaptic transmission in rat hippocampus and neocortex. *Eur J Pharmacol* 2002;449(3):221–8.
57. Buttram ME, Kurtz SP. Descriptions of gabapentin misuse and associated behaviors among a sample of opioid (Mis)users in south Florida. *J Psychoactive Drugs* 2021;53(1):47–54.
58. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? *CNS Drugs* 2014;28(6):491–6.
59. Giovannoni G, O'Sullivan JD, Turner K, et al. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *J Neurol Neurosurg Psychiatry* 2000;68(4):423–8.
60. Cilia R, Siri C, Canesi M, et al. Dopamine dysregulation syndrome in Parkinson's disease: from clinical and neuropsychological characterisation to management and long-term outcome. *J Neurol Neurosurg Psychiatry* 2014;85(3):311–8.

61. Maree RD, Marcum ZA, Saghabi E, et al. A systematic review of opioid and benzodiazepine misuse in older adults. *Am J Geriatr Psychiatry* 2016;24(11): 949–63.
62. Paulozzi LJ, Kilbourne EM, Shah NG, et al. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Med* 2012;13(1): 87–95.
63. Riggs P. Non-medical use and abuse of commonly prescribed medications. *Curr Med Res Opin* 2008;24(3):869–77.
64. Kirschner N, Ginsburg J, Sulmasy LS. Prescription drug abuse: executive summary of a policy position paper from the American College of Physicians. *Ann Intern Med* 2014;160(3):198–200.